also refer to p. 15, lines 13-29, where the Applicants affirmatively identify (S)-2-aminoethyl-L-cysteine (AEC) as an example of a L-lysine analog.

The Examiner also rejected claim 14 as being indefinite under 35 USC §112, second paragraph. Specifically, the Examiner takes exception to the language "SAM analog" used in the rejected claims.

Applicants respectfully submit that the term "SAM analog" as used in claim 14 satisfies the statutory mandate of 35 U.S.C. § 112, second paragraph. For additional clarity, however, Applicants have amended the specification at page 7 to set forth the definition noted by the Examiner appearing at page 7, lines 3-8. Applicants submit that no new matter has been added by the above amendment.

The Examiner also rejected claims 3,7,8, 11-13, and 19-22 as being indefinite under 35 USC § 112, second paragraph, because they depend upon an indefinite base claim. Applicants submit that the above amendments and comments are sufficient to remove the Examiner's rejections of the base claims and, therefore, they are sufficient to remove the instant rejection.

35 U.S.C. § 112, first paragraph

The Examiner rejected claims 1 and 3 under 35 USC § 112, first paragraph, as containing subject matter that is not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. In particular, the Examiner requires proof of deposit of strain BI282 under the requirements of the Budapest Treaty.

Upon the undersigned attorney's information and belief, strain BI282 has been deposited with the American Type Culture Collection in Rockville, Maryland, under the requirements of the Budapest Treaty. Applicants have amended page 25 of the specification to reflect this fact.

The undersigned represents that upon information and belief, the deposit has been made under the terms of the Budapest treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent.

The undersigned upon information and belief represents that the deposit will be maintained in a public depository for a period of 30 years after the date of the deposit or 5 years after the last request for a sample or for the enforceable life of the patent, whichever is longer.

The Examiner rejected claims 1, 3, and 5-22 under 35 USC § 112, first paragraph, as being non-enabling for a method of producing a biotin vitamer by culturing a bacterium in an environment enriched for a lysine precursor. The Examiner specifically takes issue with the use of a "lysine precursor" in the enriched environment for producing a biotin vitamer using a bacterium. More particularly, the Examiner requires "[g]uidance ... to help determine which lysine precursors to use with the bacterium in order to produce biotin vitamers." (Paper no. 2, at 5). The Examiner also states that "[a] large amount of experimentation would be required to identify all suitable lysine precursors." *Id.* (emphasis added.)

The Examiner is directed to Figure 4 of the captioned application because it provides at least five specific lysine precursors. In addition, Applicants refer to *Biosynthesis of the Aspartate Family of Amino Acids*, from A.L. Sonenshein et al. (eds.), *Bacillus subtilis and Other Gram-Positive Bacteria: Biochemistry, Physiology, and Molecular Genetics*, pp. 237-267, American Society for Microbiology, Washington, D.C. (1993), disclosed at page 13, lines 1-4 of the captioned application. For the Examiner's convenience, a copy of this chapter is being simultaneously submitted herewith in a Supplemental Information Disclosure Statement. The

Examiner is directed to Figure 5 on p. 246 of *Bacillus subtilis*, where about seven specific lysine precursors are disclosed.

If indeed any experimentation were to be encountered in determining which lysine precursor can function as an amino donor, it would involve using a small, finite number of compounds, i.e., lysine precursors, in a repetitious screen for biotin vitamer production, such as that taught in the captioned application. As the Federal Circuit and the Board of Appeals and Interferences have emphasized, however, such procedures do not constitute **undue** experimentation, even if they are laborious or time-consuming. *See In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) ("routine screening" of hybridomas for specific antibody IgM isotype, HBsAg specificity and 10^9 l/m affinity); *Ex parte Mark*, 12 USPQ2d 1904, 1906-7 (BPAI 1989) ("routine experimentation" necessary to determine whether disclosed procedures "would result in a [material] which is within the claims"). *See also Ex parte D*, 27 USPQ2d 1067, 1069-79 (BPAI 1993) ("routine experimentation may involve rather extensive studies without straying from 'undue' experimentation.") The standard applied by the Examiner in the outstanding office action, i.e., "large amount", is not the correct standard for making a prima facie enablement rejection.

In *Wands*, although the Federal Circuit warned that the statutory enablement requirement should not be reduced to mere numbers and percentages, it emphasized that a "2.8% rate would not require a conclusion of undue experimentation." 8 USPQ2d at 1406. Here, even if only one of the disclosed lysine precursors were successful, an 11 % success rate would be achieved (1/9).

The rejection of claims 1, 3 and 5-22 is thus erroneous to the extent it is premised upon a demand for "predicting" lysine precursors that function as amino donors. Given finite number of lysine precursors available to one skilled in the art, the fact some experimentation may have to

undertaken does not make that experimentation undue. The enablement rejection for claims 1, 3, and 5-22 should be withdrawn.

The Examiner also rejected claim 21 under 35 USC § 112, first paragraph, as being non-enabling for deregulating genes other than the *bioA* gene. The Examiner states that "[a] large amount of experimentation would be required to determine how to deregulate one of the biotin biosynthetic pathways." (Paper no. 2 at 5). More particularly, the Examiner requires "[g]uidance ... to help one skilled in the art to make such a bacterium." *Id.* at 6.

Applicants respectfully disagree with the Examiner's assertion that "[n]o guidance is provided on how to obtain a bacterium which is deregulated in at least one biotin synthetic pathway step other than *bioA* expression." *Id.*

In particular, the Examiner is directed to p. 6, line 18 -page 7, line 2 of the captioned application wherein Applicants set forth various ways to deregulate the KAPPA-to-DAPPA biosynthetic step by deregulating, i.e., overproducing DAPA aminotransferase which is the end product of the *BioA* reaction pathway.

Furthermore, p. 22, line 27 - p. 24, line 15 describe four specific instances of the deregulation of lysine production from aspartate which pathway is not involved in *bioA* expression. Moreover, Table 4 outlines the biosynthetic pathway from aspartate to lysine while, Table 7 provides a summary of the regulated enzymes in this pathway.

In this regard, the captioned application states that:

> **Four types of mutations leading to deregulated lysine synthesis are known**, 1) a DAP resistant aspartokinase I, 2) a constitutive aspartokinase II, 3) a lysine resistant DAP decarboxylase, and 4) an undefined S-2-aminoethyl-L-cystein (AEC) resistant mutation that is unlinked to any of the known lysine genes. These known mutations are summarized in Table 7. The last three all have an

> AEC resistant phenotype, and so each could be moved into a biotin production strain by transduction, transformation, or congression. (p. 23, lns. 5-14).

Applicants also refer the Examiner to p. 23, ln. 15 - p. 24, ln. 15 of the captioned application which describes the isolation of lysine deregulated mutants. Moreover, the Examiners attention is respectfully drawn to Tables 5, 6 and 8 from which it is concluded that:

> BI641 and BI642 produced a higher level of DTB than the respective parent strains in the absence of lysine, but not as much as when 6 g/l lysine was fed. Lysine biosynthesis can be further deregulated by introducing a second lysine deregulating mutation as described above. (p. 24, lns. 10-15).

Thus, Applicants respectfully submit that the captioned application clearly describes how to obtain a bacterium which is deregulated in at least one biotin synthetic pathway other than *BioA* expression. Moreover, as the Examiner has admitted that "[e]xamples of such bacteria would allow a person of skill in the art to make other deregulated pathway bacteria," (Paper no. 2 at 6) Applicants submit that the claims are enabled.

Applicants also submit that the standard applied by the Examiner in the outstanding office action, i.e., "large amount", is not the correct standard for making a *prima facie* enablement rejection. Given the numerous ways in one skilled in the art could deregulate a biotin synthetic step coupled with the specific examples provided by the Applicants, one skilled in the art would have to undertake nothing but routine experimentation to practice the claimed invention.

Applicants believe that the pending claims are presently in condition for allowance and request that the Examiner reconsider the pending claims, withdraw the rejections and quickly pass the application to issue.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231, on June 1, 1999.

Kevin C. Hooper

Respectfully submitted,

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